

Family history influences the early onset of hepatocellular carcinoma

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Abstract

AIM: To evaluate the relationship between a positive family history of primary liver cancer and hepatocellular carcinoma (HCC) development in Korean HCC patients.

METHODS: We studied a total of 2242 patients diagnosed with HCC between January 1990 and July 2008, whose family history of primary liver cancer was clearly described in the medical records.

RESULTS: Of the 2242 patients, 165 (7.4%) had a

positive family history of HCC and 2077 (92.6%) did not. The male to female ratio was 3.6:1, and the major causes of HCC were chronic hepatitis B virus (HBV) infection in 75.1%, chronic hepatitis C virus infection in 13.2% and alcohol in 3.1%. The median ages at diagnosis in the positive- and negative-history groups were 52 years (range: 29-79 years) and 57 years (range: 18-89 years), respectively ($P < 0.0001$). Furthermore, among 1713 HCC patients with HBV infection, the number of patients under 45 years of age out of 136 patients with positive family history was 26 (19.1%), whereas those out of 1577 patients with negative family history was 197 (12.5%), suggesting that a positive family history may be associated with earlier development of HCC in the Korean population ($P = 0.0028$).

CONCLUSION: More intensive surveillance maybe recommended to those with a positive family history of HCC for earlier diagnosis and proper management especially when HBV infection is present.

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Key words: Liver cancer; Hepatocellular carcinoma; Family history; Epidemiology

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INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for up to 90% of primary liver cancers. It is the fifth most common can-

cer and the third most common cause of cancer-related death worldwide^[1-3]. The major risk factors for the development of HCC include liver cirrhosis of any etiology, chronic hepatitis B virus (HBV) infection, chronic hepatitis C virus (HCV) infection, heavy alcohol consumption and non-alcoholic steatohepatitis^[2,4].

Familial clustering has been reported in many types of cancer including pancreas, colon, stomach, lung and breast cancers based on either meta-analyses or registry-based studies throughout the world^[5-9]. However, no data on familial clustering for HCC is available in Korea to date although a few studies are reported in some other countries^[10-15]. The development of HCC in Caucasian populations are reported to be less related to chronic HBV infection, but the clustering of HBV infection among family members was reported to be the major cause associated with family histories of HCC in Asia^[3,12,14,16]. Still, the impact of family history of HCC in the development of HCC remains to be determined along with the possible confounding effects of important risk factors for HCC. Here, we report a large retrospective cohort study evaluating the effect of family history of HCC on its development among Korean patients with various risk factors.

MATERIALS AND METHODS

Study population

This study was a single-hospital-based study; cases were retrospectively evaluated. The data were recruited retrospectively from the medical records of 2242 patients who had first been diagnosed with and treated for HCC between January 1990 and July 2008. Before the analysis, the diagnosis of HCC was reconfirmed based on the American Association for the Study of Liver Diseases Practice Guidelines for Management of HCC^[17], with either positive histopathology on liver biopsy and/or non-invasive criteria of hepatic imaging demonstrating one or more space-occupying lesions showing arterial hypervascularization on triphasic computed tomography and/or magnetic resonance imaging with or without an elevated alpha-fetoprotein (AFP) level.

All patients were screened for hepatitis virus infection when diagnosed with HCC, and if a patient had no evidence of chronic viral hepatitis, he or she underwent studies for autoimmune hepatitis and metabolic and/or genetic disorders such as Wilson's disease, hemochromatosis, primary biliary cirrhosis. HBV infection was diagnosed by testing for hepatitis B surface antigen, hepatitis core IgG, and HBV DNA, and HCV infection was diagnosed by testing for anti-HCV antibodies and HCV RNA; testing was performed at the central lab of Seoul St. Mary's Hospital. Alcohol-related cirrhosis was clinically diagnosed based on a compatible history of sustained alcohol consumption over 75 g/d in the absence of any other cause for liver disease.

A family history of HCC was determined based on medical records written during personal interviews on admission.

Tumor staging

Tumor staging for HCC was based on a classification system modified from the Union for International Cancer Control staging classification^[18-20].

Statistical analysis

The results are presented as frequency (*n*) and percentage for categorical data and median (minimum to maximum) for continuous data.

To compare the general characteristics according to HCC family history, categorical variables were analyzed using either the χ^2 test or Fisher's exact test, as appropriate. Continuous variables were compared using the Mann-Whitney *U*-test. To identify differences in HCC family history according to HBV and HCV infections, statistical analyses were performed by the χ^2 test, Fisher's exact test, or the Mann-Whitney *U*-test, as appropriate.

All statistical analyses were performed using SAS software, Version 9.1 (SAS Institute Inc., Cary, NC). A 2-tailed *P*-value of < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

The demographic features of the HCC patients are summarized in Table 1. A total of 2242 cases with HCC were recruited by a retrospective chart review. The number of male patients (*n* = 1765) was approximately 3.6 times that of female patients (78.7% *vs* 21.3%, respectively). The median age at the time of diagnosis was 57 years (18-89 years), and the median age at the peak incidence of HCC was in the sixth decade (*n* = 722, 32.2%) followed by the seventh (*n* = 640, 28.6%) for all cases. When classified by gender, male patients were most commonly diagnosed with HCC in their fifties, whereas female patients were most commonly diagnosed in their sixties.

The most common single cause of HCC was HBV (*n* = 1683, 75.1%); the second was HCV, and the fourth was alcohol. The group classified as "unknown" was the third largest group and included the patients with non-B, non-C, and non-alcoholic liver cirrhosis and those for whom the cause of HCC could not be identified even after thorough evaluation (Table 1). In patients with chronic hepatitis B, the peak incidence of HCC was observed in the sixth decade of life; however, it was observed 10 years later in patients for whom HCC was caused by chronic hepatitis C or alcohol (data not shown). In 32 (1.4%) of 2242 patients, more than one etiology was identified. HBV co-infection with HCV was the most common combination and affected 17 patients; HBV with alcohol was the second most common and affected 13 patients; the remaining two cases were caused by HCV with alcohol. When the patients were classified based on whether a patient had HBV infection, the HBV-positive group consisted of 1713 patients (76.4%), whereas the HBV-negative group included only 529 (23.6%) patients. The patients were then reclassified into HCV-positive and

Table 1 General characteristics of the study population *n* (%)

		Total <i>n</i> = 2242	FHx (-) <i>n</i> = 2077 (92.6%)	FHx (+) <i>n</i> = 165 (7.4%)	<i>P</i> value
Gender	Male	1765 (78.7)	1639 (78.9)	126 (76.4)	0.441
	Female	477 (21.3)	438 (21.1)	39 (23.6)	
Age	Median (min-max)	57.0 (18.0-89.0)	57.0 (18.0-89.0)	52.0 (29.0-79.0)	< 0.0001
	< 20	1 (0.1)	1 (0.1)	0 (0.0)	< 0.001
	20-29	13 (0.5)	12 (0.6)	1 (0.6)	
	30-39	112 (5.0)	99 (4.8)	13 (7.9)	
	40-49	458 (20.4)	410 (19.7)	48 (29.1)	
	50-59	722 (32.2)	661 (31.8)	61 (37.0)	
	60-69	640 (28.6)	606 (29.2)	34 (20.6)	
	≥ 80	256 (11.4)	248 (11.9)	8 (4.8)	
Etiology	HBV	1683 (75.1)	1548 (74.5)	135 (81.8)	0.236
	HCV	296 (13.2)	280 (13.5)	16 (9.6)	
	Alcohol	70 (3.1)	68 (3.3)	2 (1.2)	
	Combined	32 (1.4)	31 (1.5)	1 (0.6)	
	Others	50 (2.2)	45 (2.2)	5 (3.0)	
HBV	Unknown	111 (5.0)	105 (5.0)	6 (3.6)	0.058
	HBV (+)	1713 (76.4)	1577 (75.9)	136 (82.4)	
	HBV (-)	529 (23.6)	500 (24.1)	29 (17.6)	
	HCV (+)	315 (14.1)	298 (14.3)	17 (10.3)	
HCV	HCV (-)	1927 (85.9)	1779 (86.7)	148 (89.6)	0.15
Stage	I	185 (8.3)	167 (8.0)	18 (10.9)	0.221
	II	655 (29.2)	602 (29.0)	54 (32.7)	
	III	648 (28.9)	610 (29.4)	38 (23.1)	
	IVa and IVb	753 (33.6)	698 (33.6)	55 (33.3)	
Lab, median (min-max)	ALT (U/L)	47.0 (3.0-3505.0)	47.0 (3.0-3505.0)	47.5 (3.0-840.0)	0.987
	TB (mg/mL)	1.1 (0.1-47.6)	1.1 (0.1-47.6)	1 (0.1-26.0)	0.868
	Alb (g/dL)	3.5 (1.2-9.6)	3.5 (1.2-9.6)	3.7 (1.6-5.0)	0.106
	Platelet (× 10 ³ /μL)	121.5 (8.0-1084.0)	121.0 (18.0-1084.0)	133.0 (8.0-635.0)	0.181
Tumor markers, median (min-max)	AFP (ng/mL)	69.1 (0.0-529 470.0)	67.00 (0.0-529 470.0)	110.8 (1.1-53 606.0)	0.972
	PIVKA-II (Mau/mL)	88.0 (1.0-16 636.8)	92.0 (1.0-16 636.8)	80.0 (6.0-2000.0)	0.990

AFP: Alpha-fetoprotein; Alb: Serum albumin; ALT: Alanine transaminase; HBV: Hepatitis B virus; HCV: Hepatitis C virus; FHx: Family history; PIVKA-II: Protein induced by vitamin K deficiency-II; TB: Serum total bilirubin.

-negative groups; the HCV-positive group included only 14.1% (*n* = 315) of all patients.

By the modified International Union Against Cancer (UICC) staging classification, only 185 patients (8.3%) were diagnosed at stage I, followed by 655 (29.2%) patients at stage II, 648 (28.9%) patients at stage III, and 753 (33.6%) patients at stage IV. Thus, over half of the patients (62.5%) were diagnosed at advanced stages of HCC, including stages III and IV.

Laboratory data at diagnosis did not indicate severe hepatic dysfunction. The medians of serum alanine transaminase, serum total bilirubin, serum albumin, and platelet count were 47 U/L (3.0-3505.0), 1.1 mg/mL (0.1-58), 3.5 g/dL (1.2-4.98), and 121 500/μL (8000-1 084 000), respectively. With regard to tumor markers, the median serum AFP level was 69.1 ng/mL (0.0-529 470.0), and the median level of serum protein induced by vitamin K deficiency (PIVKA-II) was 88.0 Mau/mL (1.0-16 636.8). No statistical difference between the positive- and negative-family-history groups was found.

Family history of HCC

As shown in Table 1, 165 (7.4%) of 2242 patients had a positive family history of HCC in one or more family members, whereas 2077 (92.6%) patients had no family

history of any HCC. Because the main concern was the influence of a positive family history in the development of HCC, positive histories in the offspring of the patients were not considered. Among those 165 patients with positive family histories, 159 had a positive family history in one or more first-degree relatives, including parents and siblings. Of the remaining six patients (all of these patients as well as their mothers had HBV infection), five had a positive family history of HCC in a brother or sister of the patient's mother, and one had a positive family history in the grandmother and in an uncle on the mother's side. We considered these patients to have positive family histories because vertical transmission of HBV and its oncogenic effects on the affected individual and on his or her family members cannot be omitted in a population with a high prevalence of HBV infection. The number of patients with a positive family history in a single family member was 143. A father, a mother, or a sibling was a single family member with a history of HCC in 25, 29 and 89 patients, respectively. The number of patients with a positive family history in two or more family members were as follows: both mother and father in two, a father and a sibling in two, a mother and a sibling in 10, a mother and two siblings in one, two siblings in one, a grandmother and an uncle in one, a sibling and

Table 2 Distribution of patients with positive family history by age and tumor staging *n* (%)

	<i>n</i>	Age (yr, median)	Range	<i>P</i> value
Family members				
Father	29	53	29.0-78.0	0.101
Mother	42	48.5	33.0-79.0	
Siblings	102	39	30.0-48.0	
HBV infection				
		HBV (+)	HBV (-)	
		(<i>n</i> = 136)	(<i>n</i> = 29)	
Age	Median	52.0	57.0	0.065
	(min-max)	(30.0-78.0)	(29.0-79.0)	
	< 20	0 (0.0)	0 (0.0)	0.001
	20-29	0 (0.0)	1 (3.4)	
	30-39	12 (8.8)	1 (3.4)	
	40-49	39 (28.7)	9 (31.0)	
	50-59	56 (41.2)	5 (17.5)	
	60-69	26 (19.1)	8 (27.6)	
	70-79	3 (2.2)	5 (17.2)	
	≥ 80	0 (0.0)	0 (0.0)	
Stage	1	17 (12.5)	1 (3.4)	0.056
	2	46 (33.8)	8 (27.6)	
	3	26 (19.1)	12 (41.4)	
	4	47 (33.6)	8 (27.6)	
HCV infection				
		HCV (+)	HCV (-)	
		(<i>n</i> = 18)	(<i>n</i> = 147)	
Age	Median	54.0	52.0	0.629
	(min-max)	(29.0-75.0)	(30.0-79.0)	
	< 20	0 (0.0)	0 (0.0)	0.026
	20-29	1 (5.9)	0 (0.0)	
	30-39	1 (5.9)	12 (8.1)	
	40-49	5 (29.4)	43 (29.1)	
	50-59	3 (17.6)	58 (39.2)	
	60-69	6 (35.3)	28 (18.9)	
	70-79	1 (5.9)	7 (4.7)	
	≥ 80	0 (0.0)	0 (0.0)	
Stage	1	18 (12.2)	0 (0.0)	0.335
	2	49 (33.1)	5 (29.4)	
	3	32 (21.6)	6 (35.3)	
	4	49 (33.1)	6 (35.3)	

HBV: Hepatitis B virus; HCV: Hepatitis C virus; FHx: Family history.

an uncle in two, and a mother, grandmother, and an aunt in one. Considering 159 the patients positive family history only in the first degree relative, when grouped into HBV-positive and -negative, the median age at diagnosis of HCC was 51.5 and 57.0, respectively ($P = 0.049$).

Age at diagnosis: Regardless of the family history of HCC, both groups had a peak incidence of HCC diagnosis in their fifties. However, the median age at diagnosis was 52 years (range: 29-79 years) for those with positive family histories, which was significantly younger ($P < 0.0001$) than that for those with negative family histories (57; range: 18-89 years). In the positive-family-history group, 61 (37.0%) patients were diagnosed in their fifties, and 48 (29.1%) in their forties. In the negative-family-history group, 661 (31.8%) patients were diagnosed in their fifties, and 606 (29.2%) in their sixties ($P < 0.001$) (Table 1).

Among the patients in the positive-family-history group, the median age at diagnosis in the HBV-positive patients ($n = 136$) *vs* the HBV-negative patients ($n = 29$) was 52 *vs* 57, respectively; this difference was not sig-

nificant ($P = 0.065$). HBV-positive patients were most frequently diagnosed with HCC in their fifties ($n = 56$, 41.2%), followed by their forties ($n = 39$, 28.7%). The median age at diagnosis in the HCV-positive patients ($n = 18$) *vs* the HCV-negative patients ($n = 147$) was 54 *vs* 52 years, respectively; this difference also failed to reach statistical significance ($P = 0.629$) (Table 2).

Risk factors: HBV and HCV were two important causes of HCC development with or without a family history of HCC. Among patients with a positive family history, 135 cases were caused by HBV infection only, and 16 cases were caused by HCV only; one patient had both HBV and HCV infections (Table 1). In the negative-family-history group, 1548 (74.5%) cases were caused by HBV infection, followed by 280 (13.5%) cases of HCV infection, and these percentages were not significantly different from those found in the positive-family-history group ($P = 0.236$) (Table 1).

Among those with a positive family history of HCC, the median age at diagnosis of 136 patients with HBV infection was 52 years (range: 30-78 years), whereas that of 29 patients without HBV infection was 57 years (range: 29-79 years) ($P = 0.132$). With regard to HCV infection among those with a positive family history, the median age at diagnosis was 54 years (range: 29-75 years) in the HCV-infected group and 52 years (range: 30-79 years) in the HCV-noninfected group ($P = 0.562$) (Table 2).

Staging at diagnosis: HCC staging was based on a modified UICC staging system, with UICC stages IVa and IVb defined here as stage IV. Stages I, II, III and IV included 18 (10.9%), 54 (32.7%), 38 (23.0%) and 55 (33.4%) patients, respectively, in the positive-family-history group, and 167 (8.0%), 602 (29.0%), 610 (29.4%) and 698 (33.6%) patients, respectively, in the negative-family-history group ($P = 0.221$). When the stages were reclassified into earlier (stages I and II) *vs* advanced stages (stages III and IV), the early and advanced stages included 72 (43.6%) and 93 (56.4%) patients in the positive-family-history group and 768 (37.0%) and 1308 (63.0%) patients in the negative family history group ($P = 0.090$), respectively.

HBV infection and family history of HCC

As shown in Table 3, 1711 patients had HBV infections, and 134 (7.8%) of these had a positive family history of HCC. The median age of these 134 patients was 52 years (30-78 years), and among those without a family history ($n = 1577$, 92.1%), the median age was 57 years (range: 18.0-89.0 years), showing a significant statistical difference between the two groups ($P < 0.0001$). Among 529 patients without HBV infection, 29 (5.5%) had a positive family history of HCC, and their median age was 57 years (range: 29-79 years), whereas the remaining 500 patients without a family history had a median age of 61 years (range: 22-88 years) ($P = 0.164$). The patients were then divided into two groups based on age: a younger group (ages under 45 years) and an older group (ages 45 years or more). Among the HBV-positive patients, the numbers

Table 3 Characteristics of study subjects based on hepatitis B virus infection and family history *n* (%)

	HBV (+) (<i>n</i> = 1713)		<i>P</i> value	HBV (-) (<i>n</i> = 529)		<i>P</i> value
	FHx (+) (<i>n</i> = 136)	FHx (-) (<i>n</i> = 1577)		FHx (+) (<i>n</i> = 29)	FHx (-) (<i>n</i> = 500)	
Age, median (range)	52 (30.0-78.0)	57 (18.0-89.0)	< 0.0001	57 (29.0-79.0)	61 (22.0-88.0)	0.164
Age group						
< 45	26 (19.1)	197 (12.5)	0.028	5	57	0.244
≥ 45	110 (80.9)	1380 (87.5)		24	443	
Stage						
1	17 (12.5)	122 (7.7)	0.018	1 (2.2)	45 (9.0)	0.364
2	46 (33.8)	443 (28.1)		8 (27.6)	159 (31.8)	
3	26 (19.1)	473 (30.0)		12 (41.4)	137 (27.4)	
4	47 (34.6)	539 (34.2)		8 (27.6)	159 (31.8)	
non-HBV						
HCV				16 (55.2)	280 (56.0)	0.481
Alcohol				2 (6.9)	68 (13.6)	
Combined				0 (0.0)	2 (0.4)	
Others				5 (17.2)	45 (9.0)	
Unknown				6 (20.7)	105 (21.0)	

HBV: Hepatitis B virus; HCV: Hepatitis C virus; FHx: Family history.

of patients in the younger group with positive and negative family histories were 26 and 197, respectively, *vs* 110 and 1380, respectively, in the older group ($P = 0.028$). In the HBV-negative group with 529 patients, no significant difference was observed between the younger and older groups either in positive- (5 *vs* 24) or negative-family-history group (57 *vs* 443).

Considering the tumor staging at diagnosis, the numbers of patients with HBV infection and a positive family history were 17 (12.5%), 46 (33.8%), 26 (19.1%) and 47 (34.6%) in stages I, II, III and IV, respectively. These frequencies were significantly different ($P = 0.018$) from those among patients with HBV infection and a negative family history, for whom the corresponding numbers were 122 (7.7%), 443 (28.1%), 473 (30.0%) and 539 (34.2%). The patients without HBV infection and with a positive family history at each stage numbered 1 (3.2%), 8 (25.8%), 12 (38.7%) and 8 (32.3%), and those without HBV infection and with a negative family history numbered 45 (9.0%), 159 (31.8%), 137 (27.4%) and 159 (31.8%) in stages I, II, III and IV, respectively ($P = 0.425$).

DISCUSSION

This is the first extensive investigation of the relationship between a family history of HCC and the risk of HCC development in Korea, with further considerations regarding major risk factors for HCC development. We observed that 7.4% ($n = 165$) of 2242 patients with HCC reported having a positive family history of HCC.

The most significant finding in this study was that the median age at diagnosis was 5 years younger among patients with a positive family history than among those with a negative family history ($P < 0.0001$). Also, the age distribution was significantly different between the groups (Table 1, $P < 0.001$). The age at diagnosis of HCC had been analyzed in a previous study evaluating the association of family history of liver cancer with HCC development in the United States, but in that study, the mean age at diagnosis in patients with a positive family history (mean age: 64.1 years, $n = 21$) and in patients without a

family history (mean age: 59.9 years, $n = 156$) did not differ significantly ($P = 0.1$)^[12,21]. It was said that the lack of significant association between HCC and affected parents or offspring in the study can be related to the small numbers^[12]. On the other hand, the age difference of 5 years was significant in our study, and was younger in patients with a positive family history, we conclude that the significance was partly influenced by the large number of cases recruited in our study. Considering only the HBV-positive patients, we observed that the age at diagnosis was also significantly younger by 5 years in patients with a positive family history of liver cancer compared with those with a negative family history ($P < 0.0001$). This may be a natural corollary, as several reports have reported an association between the development of HCCs in infants and children and vertical transmission of HBV^[22,23]. From these observations, we also concluded that the age of diagnosis with HCC may be influenced by the family history of HCC regardless of whether it is related to HBV infection and that infection with HBV earlier in life is not the only factor affecting the earlier development of HCC in HBV endemic regions^[24-26]. This may also imply that a person with a history of HCC in any family member should pay special attention to screening for the development of HCC. Still, the effects of genetic backgrounds in these patients remain to be evaluated in the future.

The age recommendation for HCC surveillance in Asian males with HBV is over 40 years, and the recommendation for Asian females is over 50 years^[3,4,16,27]. In our study, when the HBV-positive patients were grouped into younger (ages under 45 years) *vs* older (ages 45 years or more) age groups, the patients with positive family histories were diagnosed with HCC at earlier ages compared with those with negative family histories ($P = 0.042$). These results are not surprising and support the common assumption that prolonged exposure to HBV seems to be a possible explanation for a relatively earlier occurrence of HCC^[21,25,26,28-32].

Another important finding in this study was the significant association between tumor staging at diagnosis and positive family history among HBV-infected patients

($P = 0.018$). Because HBV is the most common risk factor for HCC, and the vertical transmission of HBV is a medical concern in Korea (although well controlled), these findings may suggest that earlier surveillance for HCC, perhaps earlier than typically recommended, in HBV-positive patients with a positive family history of HCC may allow these patients to be diagnosed at earlier stages; this would facilitate better control of HCC and better treatment outcomes in Korean HCC patients^[33-35].

Despite the current increased efforts in HBV vaccination and in prevention of vertical transmission in Korea, HBV was the most prevalent hepatitis virus in our study population, as is expected in many Asian countries. This may reflect the effect on HCC development of vertical transmission several decades ago, before vaccination and prevention were available in Korea, and future study results may differ from ours.

This single-hospital-based study has limitations. The first is the limitation on HCC patients studied, as a single hospital cannot represent the whole country; fortunately, the general characteristics of our study subjects were not much skewed compared with other reports on HCC epidemiology in Korean patients^[30]. Second, the medical records describing family histories of primary liver cancer were solely dependent on each patient's memory. Also, the data collection was not performed prospectively, but by reviewing the medical records retrospectively, which may have led to some misclassification. Because this was, in part, a cohort study, we restricted the cases to those with clearly detailed medical records to minimize any misleading information. Third, it is possible that the findings may have been influenced by the surveillance program for HBV infection in Korea, which may have assisted in diagnosis at early ages and at early stages of HCC among patients with HBV infection and positive family histories. It is possible that chronic HBV carriers were diagnosed with HCC earlier than are patients without HBV infection because many of them had regular follow-ups at a liver clinic. However, at this point, because a patient would not be able to be diagnosed with HCC if he or she did not visit a doctor, this bias may be unavoidable unless the whole population was examined. Finally, the genetic characteristics of those who develop HCC must be evaluated in the future because not all patients with HBV infection are prone to developing HCC.

In conclusion, a positive family history of liver cancer may influence the age at diagnosis of HCC, and this difference was also in patients with HBV infection. Furthermore, we cautiously recommend more intensive check-ups earlier in life and at shorter intervals for patients who have positive family histories of liver cancer, as this may foster detection of HCC at more treatable stages.

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COMMENTS

Background

Hepatocellular carcinoma (HCC), which is the fifth most common cancer and the third most common cause of cancer-related death worldwide, has some well known risk factors for its development. The three well-known causes for this devastating disease are hepatitis B virus (HBV), hepatitis C virus (HCV), and alcoholic liver disease. Recent reports showed familial clustering of this disease based on the perinatal transmission of the HBV.

Research frontiers

Although the clustering of HBV infection among family members, which is related to vertical transmission, was reported to be the major cause associated with family histories of liver cancer and HCC, the family history of liver cancer affecting HCC development and its familial aggregation along with the possible confounding effects of important risk factors remains to be determined.

Innovations and breakthroughs

This extensive investigation revealed a significant finding that the median age at diagnosis of HCC was 5 years younger among patients with a positive family history than among those without a family history of HCC. Another important finding in this study was the significant association between tumor staging at diagnosis and positive family history in HBV-infected patients.

Applications

The study suggests that a positive family history of liver cancer may influence the age at diagnosis of HCC, and cautiously proposed that earlier surveillance for HCC, perhaps earlier than typically recommended, especially in HBV-positive patients with a positive family history of liver cancer may allow these patients to be diagnosed at earlier stages, as this may foster detection of HCC at more treatable stages.

Terminology

Familial clustering of cancers: Whether based on genetic background, environmental factors, or vertical transmission of a particular infection, familial clustering of cancers has been reported in many types of cancer, including pancreas, colon, stomach, lung and breast cancers.

Peer review

In this retrospective study, the authors have evaluated the impact of a positive family history on the development of hepatocellular carcinoma in a group of Korean patients. 7.4% of 2242 patients had a positive family history of HCC. The median age at diagnosis was significantly lower in those that had a positive family history. This result was maintained even after analyzing separately the population with non-HBV etiology. The authors conclude that a positive family history may be associated with earlier appearance of HCC, warranting a stricter surveillance.

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